INTEGRASE INHIBITOR (INI) RESISTANCE IN HIV-POSITIVE PATIENTS UNDERGOING ROUTINE TESTING

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ARV initiation in treatment-naïve patients
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• “Two nucleoside reverse transcriptase inhibitors (NRTIs) plus one of the following: ritonavir-boosted protease inhibitor (PI/r), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (INI) (1A).”¹

• Third agents:
  • Atazanavir/r
  • Darunavir/r
  • Dolutegravir
  • Elvitegravir/c
  • Raltegravir
  • Rilpivirine


• “We recommend the use of Truvada and Raltegravir as the regimen of choice for PEPSE (1B).” ¹

“Although transmitted INI-resistant virus has been described, several studies have demonstrated these are isolated cases and baseline integrase resistance testing is currently not recommended.”

- St. George’s University Hospital has been performing INI resistance (INI-R) testing routinely since September 2014
- All samples undergoing PI/NRTI/NNRTI resistance testing
- Part of a laboratory validation

Questions:

1. What is the rate of integrase inhibitor resistance in our cohort of patients?

2. What are the clinical implications?
Methods

- Retrospective review
- All INI-R reports, 1 Sept 2014 – 31 Oct 2016:
  - Mutations
  - Raltegravir, Elvitegravir, Dolutegravir resistance
- For patients attending sites that share electronic database:
  - Age, sex
  - Anti-retrovirals (ARV)
Results

• 513 samples
• 463 patients

• INI-R conferring mutations detected in
  • 58/513 samples (11.3%)
  • 51/463 patients (11.0%)
Mutations associated with INI-R (n=513)
<table>
<thead>
<tr>
<th></th>
<th>Raltegravir</th>
<th>Elvitegravir</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-level resistance</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate resistance</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Low-level resistance</td>
<td>42</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Potential low-level resistance</td>
<td>11</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Total resistance</td>
<td>58</td>
<td>58</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 1. Samples tested for INI-R (n=513)
Clinical data

- 260 samples from 227 patients
- 167 samples (64.2%) from male patients
- Median age 43 years (IQR 34-50 years)
- INI-R in 40/260 (15.4%)
ARV naïve vs. ARV experienced

- 121 samples (46.5%) from ARV-naïve patients
- 139 samples from ARV-experienced patients
  - 110 (42.3%) ARV-experienced, INI-naïve patients
  - 29 (11.2%) INI-experienced patients

INI-R
- 14/121 (11.6%) samples from ARV-naïve patients
- 18/110 (16.4%) samples from patients on non-INI ARVs
- 8/29 (27.6%) samples from patients on INI

- Rate higher in INI-experienced vs naïve patients (p=0.04)
ARV naïve (n=121)

- 25 (20.7%) started on empirical ARV
  - 17/25 – empirical regimen included INI
    - Raltegravir n=13, Dolutegravir n=4

**Patient A:**
- Empirical Raltegravir
- **E157Q** mutation, associated with low level Ral/Elv resistance
- Switched to Dolutegravir
- VL 190,000 to <40 copies/ml in 3 months.

**Patient B:**
- Empirical Dolutegravir
- **T97A** mutation: low level Ral and potential low level Elv resistance; no Dolutegravir resistance
- Remained on Dolutegravir
- VL 1x10^7 to <40 copies/ml in 4wks
ARV naïve (n=121)

• 96 did not receive empirical ARVs

  • 80/96 commenced ARVs once resistance assay results available

  • 46/80 (57.5%) – regimen contained INI
    • Dolutegravir n=23, Raltegravir n=18, Elvitegravir n=4
    • 5 had mutations
      • All were associated with resistance to Raltegravir and Elvitegravir
      • All started on Dolutegravir
On INIs (n=29)

• Raltegravir n=15, Elvitegravir n=3, Dolutegravir n=11

• INI-R 8/29 (27.6%)
  • 4/8 resistant to all 3 INIs
    • Patients taking Striibild x2 and Ral/Tru x2
    • Switched to INI-free regimen
  • 4/8 resistant to Raltegravir and Elvitegravir
    • Taking Raltegravir, switched to Dolutegravir

• None taking Dolutegravir had any resistance-conferring mutations
Patient C:

- PEPSE (Raltegravir/Truvada) 15h after unprotected SI with HIV positive man
- Seroconverted despite PEPSE
- **T97AT** mutation: associated with low-level Raltegravir resistance
- Switched to Dolutegravir
- VL <40 copies/ml within 1 month
Patient D
• Admitted with cerebral toxoplasmosis, new diagnosis HIV
  • CD4 count: 10 cells/mm³
  • VL at diagnosis: 81,600 copies/ml
  • Commenced on Tru/Raltegravir 2 ½ weeks into Toxo treatment
  • VL at 1 month: 3,050 copies/ml
  • Resistance assay: L74LM and T97A mutations -> low-level Ral and Elv resistance, potential low level Dolu resistance
  • Decision to continue
  • VL at 2 months: 219,000 copies/ml
  • Resistance assay repeated: L74LM, T97A, E92Q mutations: Intermediate Ral resistance, high level Elv resistance, low level Dolu resistance
  • Switched to a PI-based regimen
  • VL at 2 weeks: 2,840 copies/ml
  • VL at 3 months: <40 copies/ml.
Mutations in ARV-naïve vs experienced patients

ARV-naive (n=121)

- E92Q
- Q148R
- T66A
- Y143C
- E138K
- E157Q
- G140S
- G163GR
- G163K
- G163R
- L74IRM
- L74LM
- L74M
- Q95K
- T97A
- T97AS
- T97AT

% of samples with mutation

Non-INI ARV experienced (n=110)

- E92Q
- Q148R
- T66A
- Y143C
- E138K
- E157Q
- G140S
- G163GR
- G163K
- G163R
- L74IRM
- L74LM
- L74M
- Q95K
- T97A
- T97AS
- T97AT

% of samples with mutation

INI-experienced (n=29)

- E92Q
- Q148R
- T66A
- Y143C
- E138K
- E157Q
- G140S
- G163GR
- G163K
- G163R
- L74IRM
- L74LM
- L74M
- Q95K
- T97A
- T97AS
- T97AT

% of samples with mutation
Changes in rates of INI-R over time

1st September 2014

<table>
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<tr>
<th>15%</th>
<th>15.6%</th>
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31st October 2016

- Other studies shown higher rates of INI-R with increasing use\(^1-^3\)

Summary 1: high rates of INI-R

- INI-R was 11.3% in our cohort of patients
  - Highest in INI-treated patients
  - Consistent with other reports of increased INI-R in INI-experienced patients

- Also present in naïve patients
  - Suggests circulating resistance

**Recommendation 1:** Justification for performing universal INI-R testing prior to initiating ARVs

- Is it time to review current guidelines?

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Summary 2: little Dolutegravir resistance

- Resistance to Dolutegravir in only 7 samples (1.4%)  
- Almost exclusively in first gen. INI-experienced patients

**Recommendation 2:** Rationale for use of second generation INI
Summary 3: Raltegravir in PEPSE

- One patient seroconverted whilst on PEPSE with Raltegravir/Truvada
- Virus was Raltegravir-resistant (T97AT mutation)

Recommendation 3: Review the use of Raltegravir in PEPSE
- Is this still appropriate where circulating virus has >10% resistance?
Acknowledgements

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